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Deposited on: 26 April 2018

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**Validation of U.S. Mortality Prediction Models for Hospitalised Heart Failure
in The United Kingdom and Japan**

Short Title: Validation of Risk Models in Decompensated Failure

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Conflict of Interest:

Toshiyuki Nagai; None, Varun Sundaram; None, Ahmad Shoaib; None, Yasuyuki Shiraishi; None, Shun Kohsaka; None, Keiran J Rothnie; None, Susan Piper; None, Prof Theresa McDonagh; None, Dr Suzanna Hardman; None, Ayumi Goda; None, Atsushi Mizuno; None, Mitsuaki Sawano; None, Prof Alan Rigby; None, Jennifer K Quint; None, Tsutomu Yoshikawa; None, Prof Andrew L Clark; None, Prof Toshihisa Anzai; None, Prof John GF Cleland; received grants and honoraria from Amgen, Novartis, Medtronic, Philips, Servier and Stealth Biotherapeutics.

Funding: Dr. Nagai is supported by grants from the Daiichi Sankyo Foundation of Life Science and the Mochida Memorial Foundation for Medical and Pharmaceutical Research. This research was supported by a Butterfield Award for UK-Japan collaboration in Medicine & Health from The Great Britain Sasakawa Foundation.

Abstract: (248 words; Limit 250 words)

Aims: Prognostic models for hospitalised heart failure (HHF) were developed predominantly for patients of European origin in the United States of America; it is unclear whether they perform similarly in other health-care systems or for different ethnicities. We sought to validate published prediction models for HHF in the United Kingdom (UK) & Japan.

Methods and Results: Patients in the UK (894) and Japan (3,158) were prospectively enrolled and similar in terms of sex (~60% men) and median age (~77 years). Models predicted that British patients would have a higher mortality than Japanese, which was indeed true both for in-hospital [4.8% vs 2.5%] and 180-day [20.7% vs 9.5%] mortality. The model c-statistics for the published/derivation [range 0.70-0.76] and Japanese [range 0.75-0.77] cohorts were similar and higher than for the UK [0.62-0.75] but models consistently over-estimated mortality in Japan. For in-hospital mortality, OPTIMIZE-HF performed best, providing similar discrimination in published/derivation, UK and Japanese cohorts [c-indices: 0.75 (0.74-0.77); 0.75 (0.68 - 0.81) and 0.77 (0.70 - 0.83)], and least over-estimated mortality in Japan. For 180-day mortality, the c-statistics for ASCEND-HF were similar in published/derivation [0.70] and UK [0.69 (0.64 - 0.74)] cohorts but higher in Japan [0.75 (0.71 - 0.79)]; calibration was good in the UK but again over-estimated mortality in Japan.

Conclusion: Calibration of published prediction models appear moderately accurate and unbiased when applied to British patients but consistently overestimate mortality in Japan. Identifying the reason why patients in Japan have a better than predicted prognosis is of great interest.

Keywords: acute heart failure; hospitalised heart failure; mortality prediction; outcome; Japan

Introduction

The prevalence of heart failure is rising due to an ageing population and longer survival after the onset of cardiovascular diseases, including heart failure itself.¹⁻⁴ Improvements in care have failed to stem a rising tide of heart failure related hospital admissions. Annually, heart failure is the primary reason for >200,000 admissions in Japan,^{2,5} >80,000 in the United Kingdom (UK)⁶ and about one million in the United States of America (USA).⁷ Despite advances in the management of chronic heart failure, mortality amongst patients hospitalized with worsening heart failure remains high and no intervention has been convincingly shown to improve outcome.⁸⁻¹⁵

Prognostic models for hospitalized heart failure (HHF) derived from surveys, registries, and randomized clinical trials have identified many variables that are associated with outcome.¹⁶⁻²⁷ Knowing a patient's risk may help guide management, including the intensity of follow-up, the urgency of advanced interventions or the need for palliative care. Moreover, some prognostic variables, such as renal function or serum potassium concentration, might be therapeutic targets. However, prognostic models have been developed primarily in patients of European origin and in the USA. It is unclear whether these published models predict outcome in other geographic regions with different health-care systems or other ethnic groups. Important regional differences exist not only in terms of health economy, medical infrastructure and management but also patient characteristics and their adherence to medical advice and lifestyle.²⁸⁻³¹ Accordingly, we investigated the validity of five published HHF mortality prediction models for cohorts of patients enrolled in the UK and Japan.

Methods

Data sources

The UK HHF Cohort comprised registry data from two National Health Service (NHS) hospitals in London and one in Kingston-upon-Hull,³² each serving a local population of approximately 250,000 people and participating in the NHS England and Wales National Heart Failure Audit.⁶ Between 2011 and 2013, 894 patients were prospectively enrolled. Data were generally acquired within hours of admission. This was part of a national survey initiated by the NHS which provided ethical oversight.

The WET-HF (WEst Tokyo Heart Failure) registry is an ongoing, multicenter, prospective observational registry of HHF in five large academic medical centers in metropolitan Tokyo (East Japan) that enrolled 2407 patients between 2011 and 2015.³³ The NaDEF (National cerebral and cardiovascular center for acute DEcompensated heart Failure) registry enrolled 751 HHF patients prospectively at a single centre in Osaka (West Japan) between 2013 and 2015 based on the same inclusion/exclusion criteria as those in the WET-HF registry.³⁴ Data in both registries were also generally acquired within hours of admission. The study protocols of the both the Japanese registries were approved by the respective institutional review boards, and were registered at the Japanese UMIN Clinical Trial Registration (UMIN000001171 and UMIN000017024, respectively).

Patients were enrolled shortly after admission and mortality was recorded from admission providing it is reasonably accurate.

Mortality prediction models and study population

We carried out a detailed search using the MEDLINE/PubMed and EMBASE search engines and identified all the HHF mortality prediction models based on a specific search strategy

(Supplemental Appendix). This search strategy has been previously validated with high sensitivity and specificity for finding prediction research in MEDLINE.³⁵ Among these 28 models, five HHF models^{18, 19, 21, 26, 27} were chosen based on the available covariates available in both the UK and Japanese datasets (15 models were excluded due to lack of specific variables which are required to calculate the risk score and 8 models were excluded due to lack of availability of in-hospital mortality and 180 day outcomes) (**Figure 1**) for external validation in the UK and Japanese cohorts (**Table 1 and Supplementary Tables S1-1, S2, S3-1 and S4-1**).

The HHF models identified were; 1) The Get With the Guidelines-Heart Failure (GWTG-HF) risk score,¹⁸ 2) The Acute Decompensated Heart Failure National Registry (ADHERE) model,²¹ 3) The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) risk score,¹⁹ 4) The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) risk score,²⁷ 5) The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) risk score.²⁶

For each prediction model, we replicated the methods used by the original authors to calculate the predicted mortality for patients in the UK and Japanese cohorts. Racial origin was not collected but the vast majority of patients in the UK were of European origin and in Japan were Japanese. Accordingly, we did not use the ethnicity variable in the model, which applies mainly to people of African-American origin.

In the UK, blood urea nitrogen (BUN) was missing in 41% of cases, reducing the population available for analysis of all models other than OPTIME-CHF, which used serum creatinine. Therefore, we repeated all other models, substituting BUN with serum creatinine using the formula shown in **Supplemental Tables S1-2, S3-2 and S4-2**. In the ADHERE registry we

used the coefficients of BUN, systolic BP, heart rate (HR) and age from their multivariable model to calculate the log-odds of in-hospital mortality ($0.0212 \times \text{BUN} - 0.0192 \times \text{Systolic BP} + 0.0131 \times \text{HR} + 0.0288 \times \text{age} - 4.72$) as shown in the original paper. The OPTIME-CHF risk score was developed to predict 60-day mortality but because 60-day mortality was not recorded for the UK, the score was applied for 90-day mortality in each data-set.

41% (N=373) of UK patients had missing data on BUN and 27% (N=845) of Japanese patients did not have a record of New York Heart Association (NYHA) class. We therefore compared baseline characteristics and outcomes in British patients with and without BUN and in Japanese patients with and without a record of NYHA class. Survival status on days 30, 90 and 180 day was recorded rather than the precise date of death. Some patients did not have data on survival status on day 30 (N=68 in the UK, N=792 in Japan), on day 90 (N=29 in the UK, N=844 in Japan) or on day 180 (N=29 in the UK, N=906 in Japan) from the date of admission.

Statistical Analysis

Continuous variables are presented as mean \pm standard deviation when normally distributed and otherwise as median and interquartile range (IQR). Comparison of differences between groups were made using the unpaired Student's t-test or Mann-Whitney U test for continuous variables, and using chi-squared test or Fisher's exact test for dichotomous variables, where appropriate. After defining predicted mortality (predicted probability of death) for each model using the risk scores or the log odds of mortality in the logistic regression model, we assessed discriminative performance and calibration for each model. Model discrimination was assessed by calculating the c-statistic with the area under the receiver operating characteristic curve. Calibration was assessed by plotting observed against predicted mortality, coefficient of

determination (large values of R^2 indicating a better fit) and the Hosmer-Lemeshow goodness of fit statistic (smaller p-values (eg:- $P < 0.01$) indicating a poor fit). A high R^2 with a 'significant' p-value suggests that the prediction model has precision but lacks accuracy, which might be improved by introducing a 'correction factor'. All tests were two tailed, and a value of $p < 0.05$ was considered statistically significant. All analyses were performed with Stata MP 14.2 (StataCorp., College Station, TX, USA).

Results

Cohort baseline characteristics

Baseline characteristics for British (N=894) and Japanese (N=3158) patients are summarised in **Table 2**. The median ages of British (76 [IQR 67-83] years) and Japanese (78 [IQR 69-84] years) patients were similar and approximately 60% of each cohort was men. Compared to Japanese patients, British patients were more likely to have severe HF as evidenced by worse NYHA classification, lower systolic BP, lower serum sodium concentrations and higher serum concentrations of BUN and creatinine but British patients had higher body mass index. Median systolic BP in derivation cohorts of the ASCEND-HF and the OPTIME-CHF were 123 and 120 mmHg, respectively, which were more similar to British compared to Japanese patients. Median serum creatinine concentrations of patients in the GWTG-HF, the ASCEND-HF and the OPTIME-CHF were also similar to the British cohort at 1.3, 1.2 and 1.4 mg/dL, respectively but lower amongst the Japanese (1.1mg/dL). Patients in the derivation cohorts and the UK were more likely to have a reduced LVEF than in Japan. The prevalence of ischemic heart disease was higher in each of the derivation cohorts (46-59%) and amongst British patients (48%) compared to the

Japanese (25%).

Compared to Japanese patients, British patients had shorter LOHS (11 days vs 15 days $P < 0.001$); 11.1% of British and 23.8% of Japanese patients were hospitalised for >30 days. British patients had higher in-hospital (4.8% vs 2.5%, $P = 0.001$), 30-day (5.7% vs 2.6%, $P < 0.001$; 90-day (13.6% vs 6.0% $P < 0.001$) and 180-day mortality (20.7% vs 9.5%, $P < 0.001$) (**Table 3**). Despite, a higher proportion of patients with HFrEF in the UK being discharged on guideline-directed medical therapy, post-discharge mortality was significantly lower in Japan (**Table 3 and Supplementary Table S5**).

In-Patient Mortality

Risk scores for in-patient mortality for the GWTG-HF, modified-GWTG-HF and OPTIMIZE-HF and the log odds for mortality of the ADHERE and modified-ADHERE were all higher for British patients (**Table 3**) consistent with their worse actual prognosis. Model c-statistics were similar for the derivation and Japanese cohorts^{18, 19, 21} but, apart from the OPTIMIZE-HF, performed less well in the UK (**Table 4**). In the UK, model discrimination improved when BUN was replaced with creatinine, possibly because this increased the number of patients available for analysis but for Japanese patients, replacing BUN with creatinine tended to reduce discrimination (**Table 4**). Overall, the OPTIMIZE-HF model, which uses creatinine rather than BUN, provided the best discrimination with remarkably similar c-statistics for the derivation¹⁹, British and Japanese cohorts (0.753, 0.752 and 0.767 respectively).

Calibration coefficients for in-hospital mortality (**Figure 2A-C**) were also superior for the OPTIMIZE-HF compared to other models in both the UK ($R^2 = 0.76$) and Japan ($R^2 = 0.91$). Tests for goodness-of-fit consistently over-estimated mortality in all models for Japan, especially for

patients at lower risk. The OPTIMIZE-HF showed greater accuracy than other in-patient models for the UK and Japan. In Japan, substitution of BUN with creatinine reduced over-estimation of mortality leading to some improvement in fit with little effect on calibration coefficients (**Figure 3A and B**). Substitution of BUN with creatinine had little influence on model calibration in the UK cohort (**Figure 3A and B**).

Post-baseline Mortality at 30, 90 and 180 Days (Table 4, Figure 3 D-F).

For 30-day mortality (the ASCEND-HF), the c-statistic for the Japanese and derivation cohorts were similar²⁷ but lower in the UK. The model calibration coefficient was markedly higher for Japan ($R^2 = 0.82$) compared to the UK ($R^2 = 0.12$) but again over-estimated mortality in Japan. Substituting BUN with creatinine improved model precision in the UK but not Japan and improved calibration in the UK.

For 90-day (the OPTIME-CHF) mortality, the c-statistic for Japanese patients was again similar to that of the derivation cohort²⁶ but lower for British patients. Model coefficients were high for both cohorts but again over-estimated mortality in Japan; substituting BUN with creatinine had little effect on model performance for either cohort.

For 180-day mortality, the ASCEND-HF model c-statistics were similar for the derivation²⁷ and UK cohorts but higher for the Japanese. Model coefficients were high both for British ($R^2 = 0.96$) and Japanese ($R^2 = 0.95$) patients but again overestimated mortality in Japan. Substituting BUN with creatinine did not improve model performance.

Discussion

This analysis suggests that at least some published models for predicting mortality in HHF, developed predominantly for patients of European origin enrolled in the USA, provide similar prediction for patients enrolled in our registries in Japan and the UK. Indeed, the ability of the models to predict mortality was somewhat greater for Japanese compared to British patients. This suggests that the variables contributing to these models maintain their relationship to outcome in diverse health care systems and ethnicities. However, the published models consistently over-estimated mortality for HHF patients in Japan. These analyses should be confirmed and refined using other similar or larger data-sets internationally.

For in-patient mortality, the OPTIMIZE-HF performed well, in terms of discrimination and calibration, in both the UK and Japan. This is remarkable, given the very different lengths of hospital stay in the UK and Japan compared to the USA.^{17, 19, 21, 36-40} Longer hospital stays expose patients to a prolonged period at risk of events, even if they might subsequently lead to lower post-discharge mortality. Interestingly, the OPTIMIZE-HF was the only model that used serum creatinine in preference to BUN as a measure of renal dysfunction and adopted serum sodium as a “U-shaped” risk variable with 140 mEq/L as the nadir of risk.^{19, 41} In the UK, improvement in the performance of in-patient and 30-day models by substituting BUN with creatinine might simply be attributed to the ability to include more patients in the analysis. In Japan, the effect of substituting BUN for creatinine in the GWTG-HF and the ADHERE in-patient models was complex; model discrimination declined slightly but model calibration improved somewhat for the GTWG-HF and over-estimation of mortality was reduced in both models. Model coefficients for the 90- and 180-day outcome models were high for both Japan and the UK but again consistently over-estimated mortality in Japan, which was a half to a quarter of that predicted. The high model

coefficients and consistently lower than predicted mortality for Japanese patients suggests that adding a variable to adjust for ethnicity might improve model calibration. In these longer-term models, substitution of BUN with creatinine had little effect on c-statistics or calibration and only modestly reduced over-estimation of mortality in Japan. The high model coefficients and consistently lower than predicted mortality for Japanese patients suggests that adding a variable to adjust for ethnicity might improve model calibration.

Other models for HHF suggest that urea is a better marker of prognosis than creatinine.²⁴ which is consistent with the reduction in model-discrimination after substituting BUN with creatinine in Japan. However, the prognostic superiority of BUN may be modest and creatinine may serve almost as well.²⁴ Indeed, serum urea, creatinine and their ratio may all provide additive prognostic information.^{24, 42} The reason why models using BUN rather than serum creatinine should demonstrate lower model accuracy (discrimination and calibration) in British patients is uncertain. Serum creatinine reflects muscle creatinine turnover, protein intake and renal function.⁴³ BUN is also influenced by catabolic/anabolic balance but, in addition, a large proportion of urea is reabsorbed by the nephron especially if the patient is dehydrated or diuretic resistant. Greater muscle mass, differences in diet, the severity of congestion and use of higher doses of diuretics in the UK might all alter the relationships between BUN, creatinine and prognosis.

Health care systems and hospitalisation threshold vary widely across world regions; hence it is likely that risk scores provide different performance in different populations. In the present study, British patients had a worse risk profile compared to the Japanese, including lower average systolic BP, left ventricular ejection fraction and serum sodium concentration and worse renal function, although age was similar and BMI higher. The observed mortality for HHF in the UK

was similar to that predicted by the models. In other words, although the mortality associated with HHF may be higher in the UK than in some other countries, this reflects sicker patients, perhaps due to a higher threshold for admission. On the other hand, Japanese patients not only appeared less sick, perhaps reflecting a lower threshold for admission, but also had a much lower than predicted mortality, especially amongst lower risk patients. However, it is possible that models derived from "sicker" populations in the US overestimate mortality in "less sick" patients independent of the world region. We can only speculate as to the reasons for the observed difference in mortality, which may include differences in management, patients' adherence to medical advice and therapy, differences in culture, diet and lifestyle, heart failure aetiology, and genetics. Of note, mortality was higher in the UK despite a higher proportion of patients with HFrEF being discharged on guideline directed medical therapy (GDMT). One or more of the above differences might explain this anomaly.

Adding a variable to reflect a greater variety of ethnic groups might improve the performance of existing models.^{39,44} Alternatively, the influence of individual covariates could be reassessed in different ethnic groups and a new score developed but this might not capture the wider impact of ethnicity.

Prognostic models that can be applied internationally would have considerable value not only for research but also for auditing the quality of care. First, transfer of patients to a tertiary centre with advanced care / heart failure therapies such as left ventricular assisted device and transplantation can be done based on existing models of accurate mortality prediction. Second, development of effective community services for heart failure, a major thrust in the UK, means that many patients who used to be admitted to hospital for care are now managed at home or in day-care facilities. Accordingly, patients admitted to hospital are often sicker and more likely to

die. The National Heart Failure Audit for England & Wales reported an in-patient mortality for 32,991 HHF patients of 9.4% in 2013/14 (although < 3.0% if aged <65 years) which is a much higher mortality than reported in the USA (3.1% in 2010/2013)⁴⁵ or Japan (6.4% in 2007/2011).²⁸ Until an international model to assess prognosis is developed it may be impossible to determine whether poor outcome for HHF in a country reflects a high or low quality of care. Rather than starting afresh, it seems better to build on existing models, some of which performed well in this analysis. Starting with a model and only adding variables that improve it substantially or simplify it is likely to lead to faster and more certain evolution than re-inventing a new model for each new patient cohort.²⁴

Limitations

Our study population includes patients only from selected academic medical centres in Japan and Britain which may not be representative for the whole population. The mortality in our study populations was lower than that observed in the published national data in both countries. However, the difference in mortality between the two countries in our study is quite similar to difference in mortality observed in national data-sets (~40% higher mortality in UK compared to Japan). Validating prediction models in national data-sets is not currently possible since these do not record required variables including blood pressure and laboratory data.

We used the same inclusion/exclusion HHF criteria for both Japanese registries (WET-HF and NaDEF) to increase the power of the analysis and generalizability of the results, although some differences in characteristics and outcomes were observed between these data-sets (**Supplementary Table S6**).

Renal function and NYHA functional class are key determinants of prognosis in patients

with HF.⁴⁶ The prediction models included in this analysis, with the exception of the OPTIMIZE-HF, used BUN as a measure of renal dysfunction but this variable was missing in many patients from the UK. Moreover, NYHA functional class was often missing in Japanese patients. Some significant differences in baseline characteristics and outcomes were observed amongst patients who did or did not have these data recorded. Patients who had a missing BUN appeared sicker while patients without a record of NYHA class appeared less sick (**Supplementary Table S7**). However, supplementary analysis restricted only to patients without missing BUN and NYHA data and using BUN showed similar results to the main analysis (**Supplementary Table S8 and Supplementary Figure S1**).

Fortunately, serum creatinine was available in >99% allowing many more patients to be included in the analysis when used instead of BUN. This may explain why the OPTIMIZE-HF model performed well in the UK and why substitution of BUN with creatinine improved the performance of some models for the UK cohort. The failure of similar substitution to improve discrimination in Japanese patients supports the notion that the improvement in the c-statistic in the UK was due to the inclusion of more patients rather than creatinine being a superior prognostic marker.

We excluded 23 published models from 28 identified mortality prediction models either because our data lacked specific variables that the models required or because they did not report on in-hospital or 180-day mortality.

The OPTIME-CHF model was developed for 60-day mortality, but as only 90-day mortality was recorded in the UK, we used this time-frame instead. As most deaths occurring in the first 90-days will have occurred within 60-days, this is unlikely to make a major difference.

The OPTIME-CHF and the ASCEND-HF models were developed on patients who

consented to participate in a randomized controlled trial. Such patients may not be epidemiologically representative and the effects of excluding patients who were not approached to participate or who declined is uncertain.

Conclusions:

Our analysis shows that existing prediction models predominantly derived from USA population and healthcare system provide fairly good discrimination for mortality amongst patients with HHF in the UK and Japan but overestimate mortality in Japan. Existing models could provide the basis for a universal mortality prediction model for HHF but might require modification depending on ethnicity. Further external validation of prediction models in diverse health care systems should be considered prior to application in routine clinical practice. Identifying the reason why patients in Japan have a better than predicted prognosis would be of great interest.

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Figure Legends

Figure 1-- Search strategy for the published HHF mortality prediction models. AUC = area under the curve; HHF = hospitalised due to worsening symptoms and signs of heart failure.

Figure 2-- Calibration plot. Predicted compared to observed mortality for the published models. The line shows the line of perfect calibration. Dots represent mortality for patients stratified by predicted mortality for each cohort. P-values are for Hosmer-Lemeshow goodness-of-fit tests. ADHERE = Acute Decompensated Heart Failure National Registry; ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; GWTG-HF = Get With the Guidelines-Heart Failure; OPTIME-CHF = Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.

Figure 3-- Calibration plot for modified published prediction models substituting BUN with creatinine. Predicted compared to observed mortality for the published models. The line shows the line of perfect calibration. Dots represent mortality for patients stratified by predicted mortality for each cohort. P-values are for Hosmer-Lemeshow goodness-of-fit tests. Abbreviations as in Figure 2.

Supplemental Figure S 1-- Calibration plot, restricted only to patients without missing BUN (in the UK) and NYHA (in Japan) data. ADHERE = Acute Decompensated Heart Failure National Registry; ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; GWTG-HF = Get with the Guidelines-Heart Failure; OPTIME-CHF = Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure.

Table 1 Published Mortality prediction models and the variables imputed on those models

Variables	GWTG-HF	ADHERE	OPTIMIZE-HF	ASCEND-HF	OPTIME-CHF
Reference	18	21	19	27	26
Published year	2010	2005	2008	2015	2004
Type of study	Registry	Registry	Registry	RCT	RCT
Number of patients	71,284	33,046	37,548	7,141	949
Number of Hospitals	287	263	259	398	80
Country	USA	USA	USA	#International	USA
Mortality	Hospital	Hospital	Hospital	30-day & 180-day	60-day
Age	✓	✓	✓	✓	✓
Systolic BP	✓	✓	✓	✓	✓
Sodium	✓		✓	✓	✓
<i>*BUN</i>	✓	✓		✓	✓
SCr			✓		
Heart rate		✓			
<i>*Black race</i>	✓				
COPD	✓				
LVSD			✓		
Primary cause for admission (HF/other)			✓		
NYHA Class IV				✓	✓

- **Modified GWTG-HF score:** *Race was not available in the UK patients; because the assigned score was very low (0-3) and around 3% of population in England is British black, we assigned score “3” in all UK patients. BUN was replaced with creatinine
- **Modified ASCEND-HF score:** BUN replaced with creatinine
- **Modified OPTIME-CHF score:** BUN replaced with creatinine
**41.7% of patients in the UK had missing BUN value and hence was replaced with creatinine*
 # North America (44.9%), Europe (20.8%), Asia Pacific (24.9%), South America (9.4%)

ADHERE = Acute Decompensated Heart Failure National Registry; ASCEND-HF = Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; BP = blood pressure; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; GWTG-HF = Get With the Guidelines-Heart Failure; LVSD = left ventricular systolic dysfunction; NYHA = New York Heart Association; OPTIME-CHF = Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; SCr = serum creatinine; UK = United Kingdom; USA = United States of America; RCT= Randomized clinical trial

Table 2 Baseline characteristics

Variable	% Missing UK/Japan	UK N=894	Japan N=3158	P-value
Age, years	0.1/0.0	76 (67-83)	78 (69-84)	<0.001
Male sex, n (%)	0/6.8	555 (62)	1744 (59)	0.13
BMI	18.1/8.6	28 (25-33)	23 (20-26)	<0.001
NYHA III or IV, n (%)		802 (92)	1889 (82)	<0.001
NYHA IV, n (%)	2.7/26.8	252 (29)	1077 (47)	<0.001
Systolic BP, mmHg	0.6/15.1	129 (110-149)	136 (118-159)	<0.001
Heart rate, /min	0.7/15.4	86 (72-106)	90 (72-110)	0.016
LVEF \leq 45%, %	12.6/18.7	560 (72)	1377 (54)	<0.001
Comorbidities, n (%)				
Ischemic heart disease	0/0	433 (48)	778 (25)	<0.001
Diabetes mellitus	0.1/0.1	297 (33)	1187 (38)	0.017
Hypertension	0.1/0.2	512 (57)	2312 (73)	<0.001
COPD/Asthma	0/18.4	221 (25)	141 (5)	<0.001
Atrial fibrillation	0.6/18.4	374 (41)	1305 (51)	<0.001
Stroke	1.3/18.6	88 (10)	457 (18)	<0.001
Laboratory data				
Hemoglobin, g/dL	43.7/0.4	12.3 (10.9-13.6)	11.8 (10.1-13.3)	<0.001
Sodium, mEq/L	0.1/0.5	138 (135-141)	140 (137-142)	<0.001
Potassium, mEq/L	2.1/0.5	4.4 (4.0-4.8)	4.3 (3.9-4.7)	<0.001
BUN, mg/dL	41.7/0.5	24.7 (16.5-38.9)	22.7 (16.7-33.0)	0.004
Creatinine, mg/dL	0.5/0.6	1.3 (1.0-1.7)	1.1 (0.8-1.5)	<0.001
eGFR, mL/min/1.73m ²	0.5/7.3	52 (36-73)	66 (43-89)	<0.001
CRP, mg/dL	22.5/0.0	1.5 (0.5-3.5)	0.5 (0.1-1.8)	<0.001
Medications at discharge, n (%)				
ACE-Is or ARBs	3158	682 (83)	1945 (63)	<0.001
Beta blockers	8.1/1.9	640 (78)	2268 (73)	0.007
MRAs	7.2/7.7	424 (51)	962 (33)	<0.001
Diuretics	6.5/7.3	748 (89)	2070 (71)	<0.001

Digitalis	5.6/2.1	203 (24)	251 (8)	<0.001
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Values are n (%) or median (interquartile range), unless otherwise indicated.

ACE-I = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; CRP = C - reactive protein; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NYHA = New York Heart Association.

Table 3 Risk score and classification, predicted probability of death, duration of hospital stay, and actual mortality

Variable	UK N=894	Japan N=3158	P-value
Risk scores or log odds of mortality (for ADHERE)			
GWTG-HF for In-hospital death			
Score	45 ± 9	41 ± 8	<0.001
Predicted probability of death, %	8.1	6.6	-
Modified GWTG-HF for In-hospital death			
Modified score	48 ± 9	46 ± 9	<0.001
Predicted probability of death, %	4.9	4.1	-
ADHERE for In-hospital death			
Score	-3.1 ± 0.9	-3.4 ± 0.9	<0.001
Predicted probability of death, %	8.0	7.0	-
Modified ADHERE for In-hospital death			
Modified score	-3.9 ± 0.7	-4.0 ± 0.7	0.008
Predicted probability of death, %	4.8	4.6	-
OPTIMIZE-HF for In-hospital death			
Score	35 ± 8	34 ± 7	<0.001
Predicted probability of death, %	5.1	4.4	-
ASCEND-HF for 30-day death			
Score	3 (2-5)	3 (2-4)	<0.001
Predicted probability of death, %	5.6	5.2	-
Modified ASCEND-HF for 30-day death			
Modified score	3 (2-5)	3 (2-4)	<0.001
Predicted probability of death, %	5.6	5.0	-
OPTIME-CHF for 90-day death			
Score	186 ± 45	173 ± 44	<0.001
Predicted probability of death, %	16.1	13.8	-
Modified OPTIME-CHF for 90-day death			
Modified score	174 ± 38	164 ± 38	<0.001
Predicted probability of death, %	13.3	11.4	-
ASCEND-HF for 180-day death			

Predicted probability of death, %	23.7	20.7	-
Modified ASCEND-HF for 180-day death			
Predicted probability of death, %	20.5	17.9	-
Length of Hospital Stay, days	11 (7-18)	15 (10-24)	<0.001
Length of Hospital Stay >30 days, %	11.1	23.8	<0.001
Actual mortality			
In-hospital	43 (4.8)	80 (2.5)	<0.001
30-day	47 (5.7)	62 (2.6)	<0.001
90-day	118 (13.6)	138 (6.0)	<0.001
180-day	179 (20.7)	214 (9.5)	<0.001

Values are n (%), or mean \pm SD, or median (interquartile range), unless otherwise indicated.

Abbreviations as in Table 1.

Table 4 Discriminative value of risk models

	Derivation cohort	UK	Japan
Models	C-statistic (95% CI)	C-statistic (95% CI)	C-statistic (95% CI)
In-hospital			
GWTG-HF	0.75	0.669 (0.594 - 0.737)	0.771 (0.710 - 0.832)
Modified GWTG-HF		0.722 (0.653 - 0.791)	0.758 (0.696 - 0.820)
ADHERE	0.759	0.663 (0.590 - 0.735)	0.755 (0.694 - 0.816)
Modified ADHERE		0.695 (0.622 - 0.768)	0.689 (0.624 - 0.755)
OPTIMIZE-HF	0.753 (0.741-0.765)	0.752 (0.683 - 0.810)	0.767 (0.702 - 0.832)
30-day			
ASCEND-HF	0.75	0.619 (0.521 - 0.717)	0.750 (0.677 - 0.822)
Modified ASCEND-HF		0.661 (0.592 - 0.730)	0.731 (0.659 - 0.802)
90-day			
OPTIME-CHF	0.76	0.673 (0.607 - 0.739)	0.751 (0.706 - 0.796)
Modified OPTIME-CHF		0.701 (0.650 - 0.753)	0.730 (0.683 - 0.777)
180-day			
ASCEND-HF	0.70	0.689 (0.637 - 0.742)	0.748 (0.712 - 0.785)
Modified ASCEND-HF		0.689 (0.647 - 0.731)	0.734 (0.697 - 0.770)

Other abbreviations as in Table 1.

Figure 1

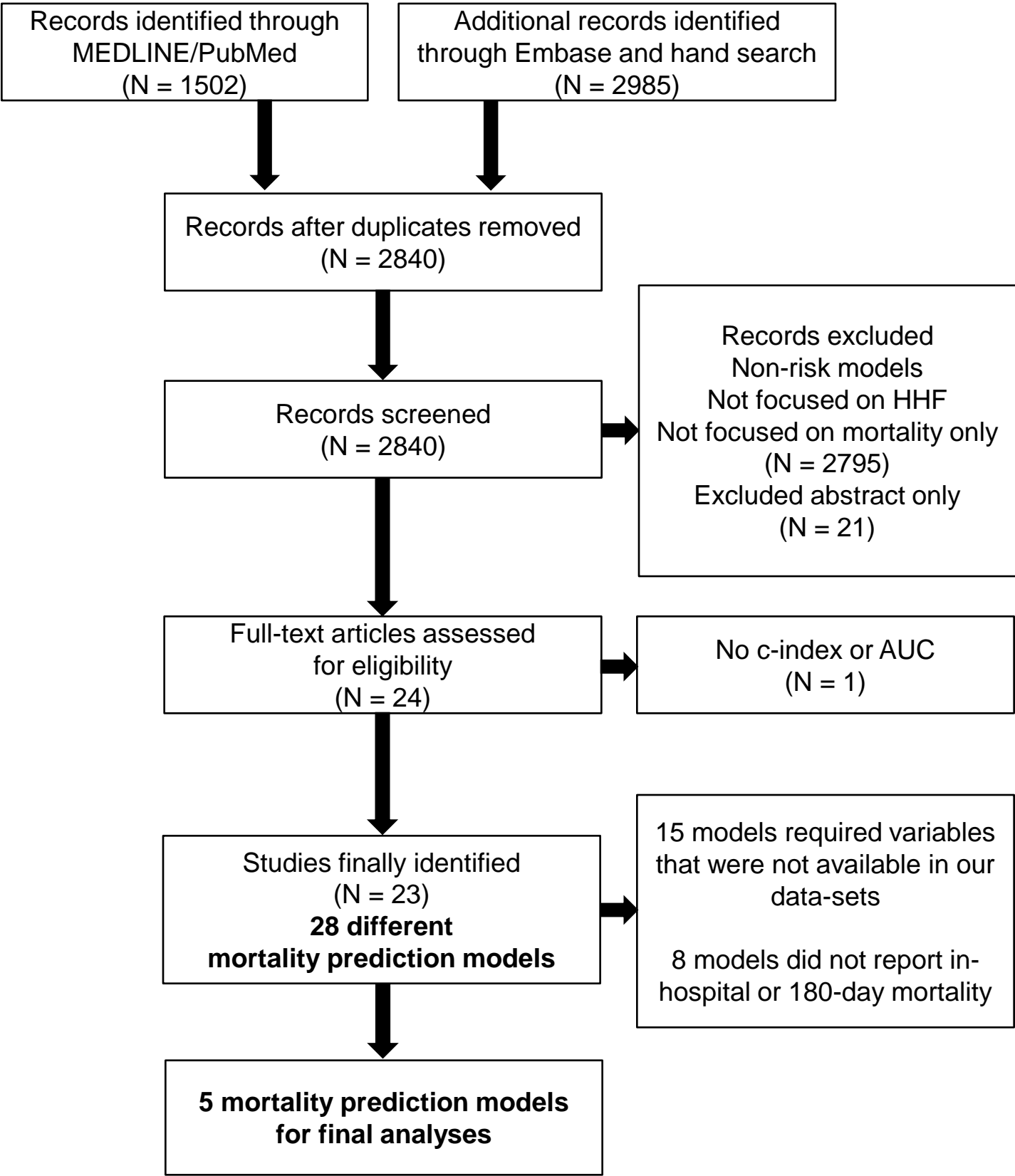


Figure 2

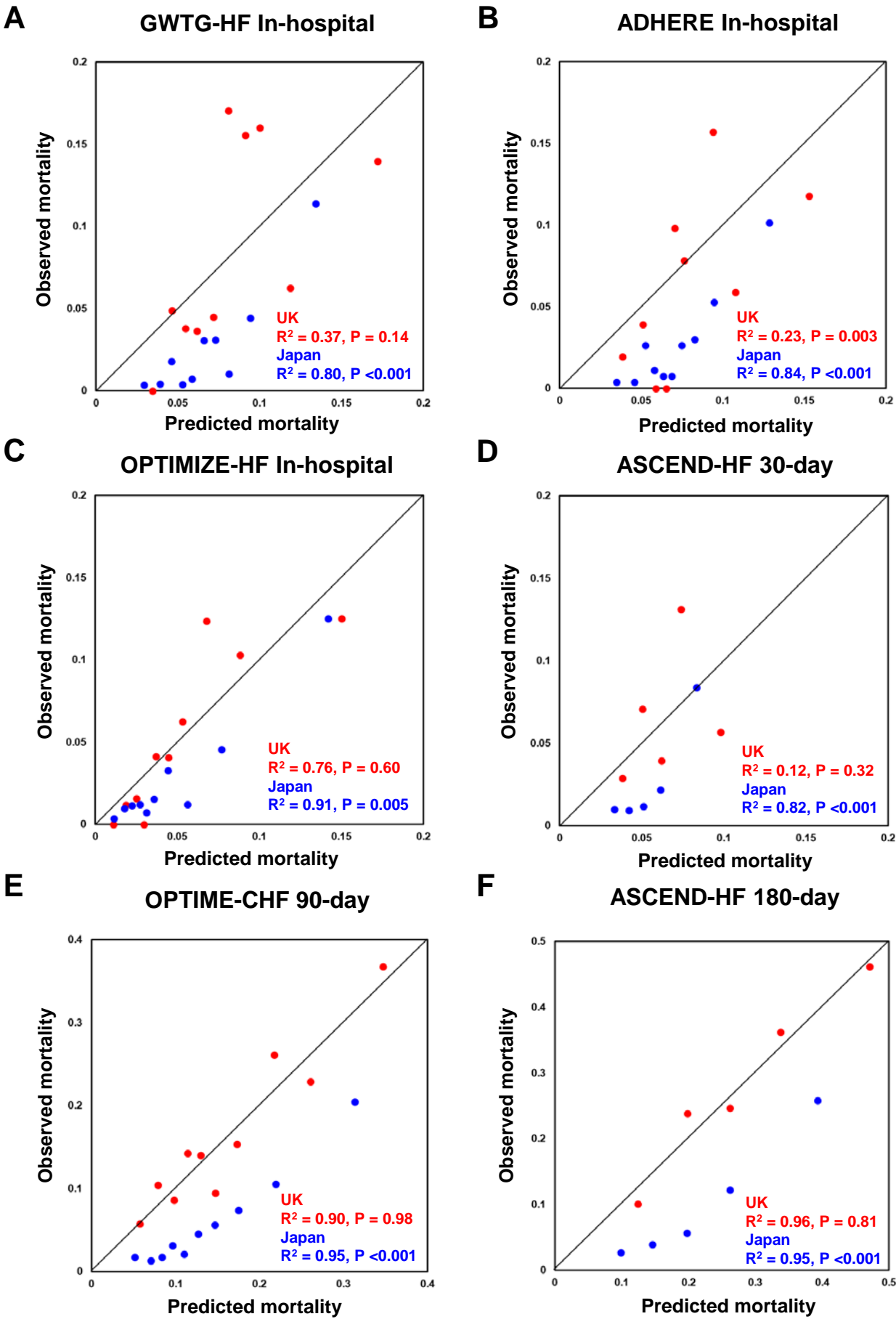
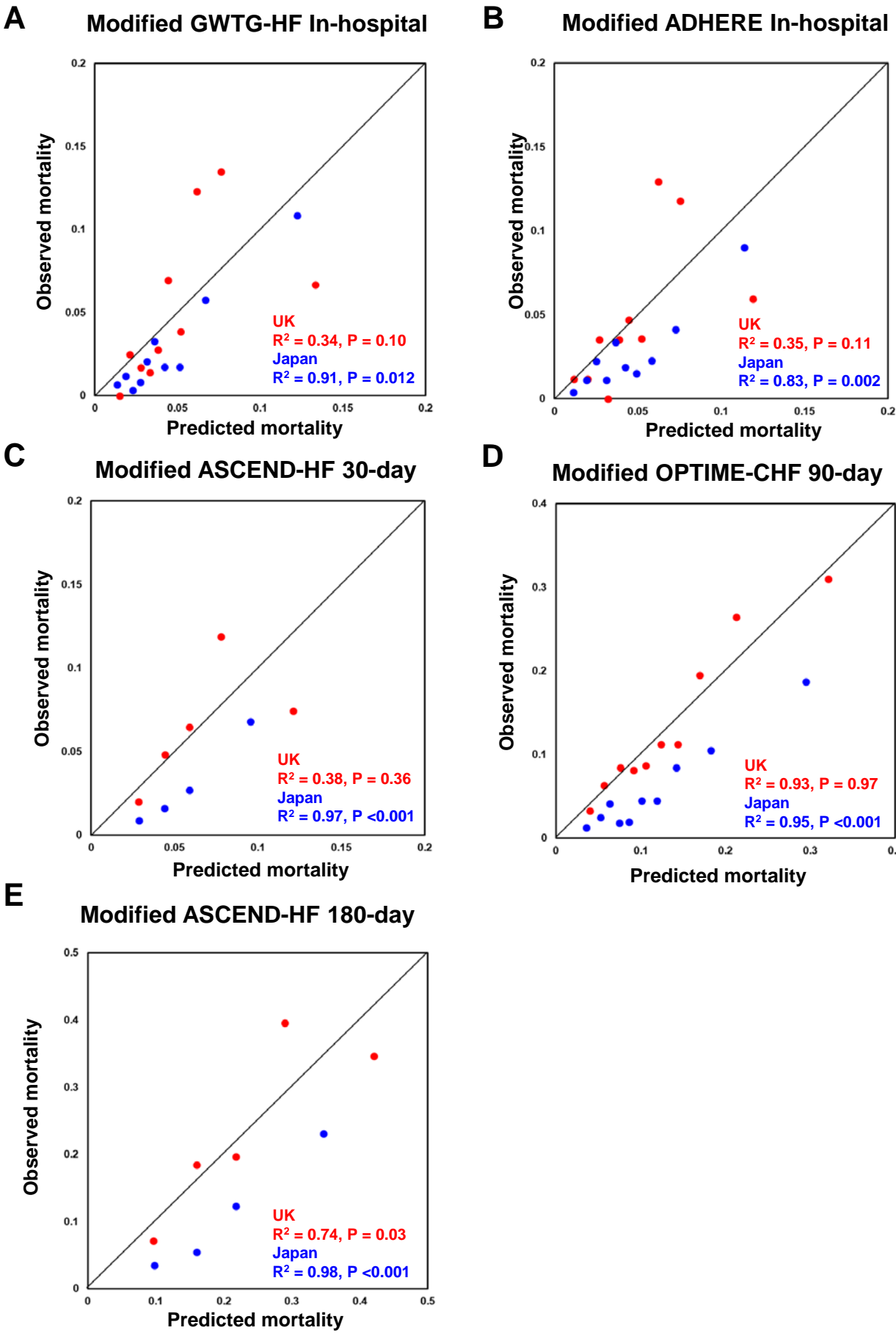


Figure 3



Supplementary Tables

Supplementary Table S1-1 GWTG-HF score

Age, yrs	Score	Heart rate, beats/min	Score	SBP, mmHg	Score	Sodium, mEq/L	Score	BUN, mg/dl	Score	Black race	Score	COPD	Score
≤19	0	≤79	0	50-59	28	≤130	4	≤9	0	Yes	0	Yes	2
20-29	3	80-84	1	60-69	26	131	3	10-19	2	No	3	No	0
30-39	6	85-89	3	70-79	24	132	3	20-29	4				
40-49	8	90-94	4	80-89	23	133	3	30-39	6				
50-59	11	95-99	5	90-99	21	134	2	40-49	8				
60-69	14	100-104	6	100-109	19	135	2	50-59	9				
70-79	17	≥105	8	110-119	17	136	2	60-69	11				
80-89	19			120-129	15	137	1	70-79	13				
90-99	22			130-139	13	138	1	80-89	15				
100-109	25			140-149	11	≥139	0	90-99	17				
≥110	28			150-159	9			100-109	19				
				160-169	8			110-119	21				
				170-179	6			120-129	23				
				180-189	4			130-139	25				
				190-199	2			140-149	27				
				≥200	0			≥150	28				

BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; SBP = systolic blood pressure.

Table S1-2 Modified GWTG-HF score

Age, yrs	Score	Heart rate, beats/min	Score	SBP, mmHg	Score	Sodium, mEq/L	Score	SCr, mg/dl	Score	Black race	Score	COPD	Score
≤19	0	≤79	0	50-59	28	≤130	4	0	0	Yes	0	Yes	2
20-29	3	80-84	1	60-69	26	131	3	0-0.49	2	No	3	No	0
30-39	6	85-89	3	70-79	24	132	3	0.50-0.74	4				
40-49	8	90-94	4	80-89	23	133	3	0.75-0.99	6				
50-59	11	95-99	5	90-99	21	134	2	1.00-1.24	8				
60-69	14	100-104	6	100-109	19	135	2	1.25-1.49	9				
70-79	17	≥105	8	110-119	17	136	2	1.50-1.74	11				
80-89	19			120-129	15	137	1	1.75-1.99	13				
90-99	22			130-139	13	138	1	2.00-2.24	15				
100-109	25			140-149	11	≥139	0	2.25-2.49	17				
≥110	28			150-159	9			2.50-2.74	19				
				160-169	8			2.75-2.99	21				
				170-179	6			3.00-3.24	23				
				180-189	4			3.25-3.49	25				
				190-199	2			3.50-3.74	27				
				≥200	0			≥3.75	28				

COPD = chronic obstructive pulmonary disease; SBP = systolic blood pressure; SCr = serum creatinine.

Supplementary Table S2 OPTIMIZE-HF score

Age, yrs	Score	Heart rate, beats/min	Score	SBP, mmHg	Score	Sodium, mEq/L	Score	SCr, mg/dl	Score	Primary cause of admission	Score	LVSD	Score
20	0	65	0	50	22	110	13	0	0	HF	0	No	0
25	2	70	1	60	20	115	11	0.5	2	Other	3	Yes	1
30	3	75	1	70	18	120	9	1	5				
35	5	80	2	80	16	125	7	1.5	7				
40	6	85	3	90	14	130	4	2	10				
45	8	90	4	100	12	135	2	2.5	12				
50	9	95	4	110	10	140	0	3	15				
55	11	100	5	120	8	145	2	3.5	17				
60	13	105	6	130	6	150	4						
65	14	110	6	140	4	155	6						
70	16			150	2	160	8						
75	17			160	0	165	10						
80	19					170	12						
85	20												
90	22												
95	24												

HF = heart failure; LVSD = left ventricular systolic dysfunction; SBP = systolic blood pressure; SCr = serum creatinine.

Supplementary Table S3-1 ASCEND-HF score

Age, yrs	Score	SBP, mmHg	Score	Sodium, mEq/L	Score	BUN, mg/dl	Score	Dyspnea at rest	Score
>70	1	<130	1	<138	1	>25	1	Yes	1
>80	2	<100	2	<134	2	>40	2	No	0
						>80	3		

BUN = blood urea nitrogen; SBP = systolic blood pressure.

Table S3-2 Modified ASCEND-HF score

Age, yrs	Score	SBP, mmHg	Score	Sodium, mEq/L	Score	SCr, mg/dl	Score	Dyspnea at rest	Score
>70	1	<130	1	<138	1	>1	1	Yes	1
>80	2	<100	2	<134	2	>2	2	No	0
						>3	3		

SBP = systolic blood pressure; SCr = serum creatinine.

Supplementary Table S4-1 OPTIME-CHF score

Age, yrs	Score	SBP, mmHg	Score	Sodium, mEq/L	Score	BUN, mg/dl	Score	NYHA Class IV	Score
20	0	80	94	115	79	5	10	No	0
30	8	90	86	120	69	10	20	Yes	23
40	17	100	77	125	59	15	30		
50	25	110	69	130	49	20	40		
60	33	120	60	135	30	25	50		
70	41	130	51	140	20	30	60		
80	50	140	43	145	10	35	70		
90	58	150	34	150	0	40	80		
		160	26			45	90		
		170	17			50	100		
		180	9						
		190	0						

BUN = blood urea nitrogen; NYHA = New York Heart Association; SBP = systolic blood pressure.

Table S4-2 Modified OPTIME-CHF score

Age, yrs	Score	SBP, mmHg	Score	Sodium, mEq/L	Score	SCr, mg/dl	Score	NYHA Class IV	Score
20	0	80	94	115	79	0	-	No	0
30	8	90	86	120	69	0.4	20	Yes	23
40	17	100	77	125	59	0.8	30		
50	25	110	69	130	49	1.2	40		
60	33	120	60	135	30	1.6	50		
70	41	130	51	140	20	2	60		
80	50	140	43	145	10	2.4	70		
90	58	150	34	150	0	2.8	80		
		160	26			3.2	90		
		170	17			3.6	100		
		180	9						
		190	0						

NYHA = New York Heart Association; SBP = systolic blood pressure; SCr = serum creatinine.

Supplementary Table S5 Medications at discharge in patients with LVEF $\leq 45\%$

Variable	UK N=318	Japan N=1148	P-value
Medications at discharge, n (%)			
ACE-Is or ARBs	257 (90)	784 (70)	<0.001
Beta blockers	243 (84)	938 (84)	0.82
MRAs	185 (64)	455 (41)	<0.001
Diuretics	260 (90)	891 (80)	<0.001
Digitalis	99 (33)	112 (10)	<0.001

Values are n (%).

ACE-I = angiotensin converting enzyme; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists.

Supplementary Table S6 Baseline characteristics and outcomes between Japanese databases

Variable	WET-HF N=2407	NaDEF N=751	P-value
Age, years	78 (68-84)	78 (70-84)	0.98
Male sex, n (%)	1295 (59)	449 (60)	0.74
NYHA IV, n (%)	730 (45)	347 (51)	0.007
Systolic BP, mmHg	137 (118-160)	135 (117-157)	0.38
Heart rate, /min	90 (73-111)	88 (71-108)	0.015
LVEF \leq 45%, %	962 (50)	415 (64)	<0.001
Comorbidities, n (%)			
Ischemic heart disease	559 (23)	219 (29)	<0.001
Diabetes mellitus	914 (38)	273 (36)	0.43
Hypertension	1760 (73)	552 (74)	0.91
COPD/Asthma	109 (6)	32 (4)	0.085
Atrial fibrillation	927 (51)	378 (50)	0.85
Stroke	263 (14)	194 (26)	<0.001
Laboratory data			
Sodium, mEq/L	140 (137-142)	140 (138-142)	0.042
Potassium, mEq/L	4.3 (3.9-4.7)	4.2 (3.8-4.6)	0.090
BUN, mg/dL	22 (17-32)	24 (17-34)	0.011
Creatinine, mg/dL	1.0 (0.8-1.5)	1.1 (0.9-1.6)	<0.001
Medications at discharge, n (%)			
ACE-Is or ARBs	1428 (60)	517 (70)	<0.001
Beta blockers	1742 (74)	526 (72)	0.27
MRAs	634 (29)	328 (45)	<0.001
Diuretics	1482 (68)	588 (80)	<0.001
Digitalis	165 (7)	86 (12)	<0.001
Length of Hospital Stay, days	14 (9-22)	20 (14-28)	<0.001
Death			
In-hospital	64 (2.7)	16 (2.1)	0.42
30-day	49 (2.9)	13 (1.9)	0.17

90-day	106 (6.5)	32 (4.7)	0.104
180-day	170 (10.7)	44 (6.7)	0.003

Values are n (%) or median (interquartile range), unless otherwise indicated.

ACE-I = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; CRP = C - reactive protein; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NYHA = New York Heart Association.

Supplementary Table S7 Baseline characteristics and outcomes between included and excluded patients

Variable	UK		P-value	Japan		P-value
	With BUN N=521	Without BUN N=373		With NYHA N=2313	Without NYHA N=845	
Age, years	78 (71-84)	73 (60-82)	<0.001	78 (68-84)	79 (70-85)	<0.001
Male sex, n (%)	336 (64)	219 (59)	0.079	1400 (61)	344 (55)	0.008
BMI	28 (25-33)	28 (24-33)	0.84	23 (20-26)	23 (20-26)	0.035
NYHA III or IV, n (%)	443 (88)	359 (98)	<0.001	1889 (82)	-	-
NYHA IV, n (%)	58 (12)	194 (53)	<0.001	1077 (47)	-	-
Systolic BP, mmHg	125(109-145)	133 (115-153)	<0.001	136 (117-158)	138(120-160)	0.42
Heart rate, /min	85 (71-104)	91 (73-110)	0.008	90 (72-110)	92 (73-112)	0.39
LVEF \leq 45%, %	318 (67)	242 (80)	<0.001	1148 (54)	229 (53)	0.72
Comorbidities, n (%)						
Ischemic heart disease	285 (55)	148 (40)	<0.001	637 (28)	141 (17)	<0.001
Diabetes mellitus	179 (34)	118 (32)	0.41	824 (35)	373 (44)	<0.001
Hypertension	293 (56)	219 (59)	0.43	1572 (68)	740 (88)	<0.001
COPD/Asthma	125 (24)	96 (26)	0.55	125 (5)	16 (6)	0.75
Atrial fibrillation	236 (46)	138 (37)	0.009	1180 (51)	125 (47)	0.19
Stroke	53 (10)	35 (9)	0.61	406 (18)	51 (19)	0.65
Laboratory data						
Sodium, mEq/L	138 (135-140)	139 (136-141)	<0.001	140 (138-142)	140 (137-142)	0.004
Potassium, mEq/L	4.4 (4.0-4.8)	4.4 (4.1-4.9)	0.24	4.3 (3.9-4.7)	4.2 (3.8-4.6)	<0.001
BUN, mg/dL	25 (17-39)	N/A	N/A	23 (17-32)	23 (17-37)	0.17
Creatinine, mg/dL	1.3 (1.0-1.7)	1.3 (0.9-1.7)	0.63	1.1 (0.8-1.5)	1.1 (0.7-1.7)	0.93
Medications at discharge, n (%)						
ACE-Is or ARBs	379 (80)	303 (87)	0.007	1462 (65)	483 (58)	<0.001
Beta blockers	370 (78)	270 (78)	0.87	1684 (75)	584 (70)	0.008
MRAs	243 (51)	181 (51)	0.87	787 (31)	165 (25)	<0.001
Diuretics	419 (88)	329 (92)	0.048	1765 (78)	305 (46)	<0.001

Digitalis	143 (30)	58 (16)	<0.001	209 (9)	42 (5)	<0.001
Length of Hospital Stay, days	11 (7-18)	11 (6-17)	0.43	16 (11-24)	12 (7-21)	<0.001
Death						
In-hospital	43 (8.3)	0 (0.0)	<0.001	61 (2.6)	19 (2.3)	0.54
30-day	27 (5.8)	20 (5.6)	0.90	50 (2.5)	12 (3.5)	0.26
90-day	84 (16.6)	34 (9.5)	0.003	106 (5.4)	32 (9.6)	0.002
180-day	122 (24.1)	57 (15.9)	0.003	169 (8.7)	45 (14.1)	0.002

Values are n (%) or median (interquartile range), unless otherwise indicated.

ACE-I = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; CRP = C - reactive protein; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NYHA = New York Heart Association.

Supplementary Table S8 Discriminative value of risk models, restricted only to patients without missing BUN (in the UK) and NYHA (in Japan) data

	Derivation cohort	UK (N=521)	Japan (N=2313)
Models	C-statistic (95% CI)	C-statistic (95% CI)	C-statistic (95% CI)
In-hospital			
GWTG-HF	0.75	0.682 (0.593 - 0.771)	0.766 (0.700 - 0.832)
ADHERE	0.759	0.665 (0.572 - 0.757)	0.750 (0.684 - 0.816)
OPTIMIZE-HF	0.753 (0.741-0.765)	0.723 (0.640 - 0.806)	0.759 (0.689 - 0.830)
30-day			
ASCEND-HF	0.75	0.619 (0.521 - 0.717)	0.746 (0.670 - 0.822)
90-day			
OPTIME-CHF	0.76	0.674 (0.600 - 0.747)	0.735 (0.682 - 0.787)
180-day			
ASCEND-HF	0.70	0.676 (0.615 - 0.736)	0.733 (0.692 - 0.774)

Other abbreviations as in Table 1.

Supplementary Figure S1

